

# Vitamin D and Influenza

Warfighter Nutrition: Advanced Technologies and  
Opportunities”

Uniformed Services University of the Health Sciences

Health Affairs and DARPA co-hosts

Day 2 (16 July 2008)

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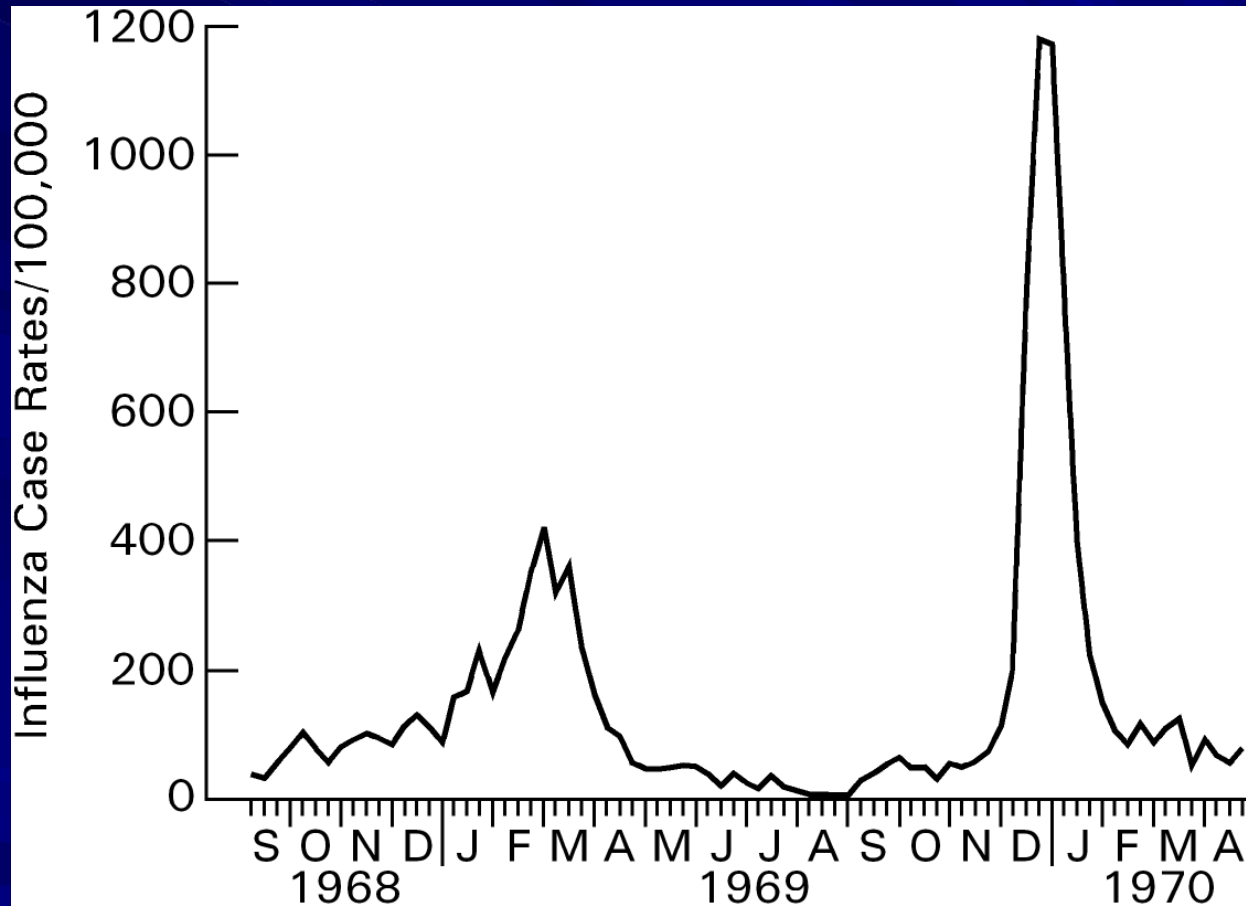
# Research associates vitamin D with:

- All cause mortality
- Heart disease
- Diabetes
- Cancer
- Osteoporosis
- Athletic ability
- Depression

# Historical studies: cod liver oil prevents respiratory infections

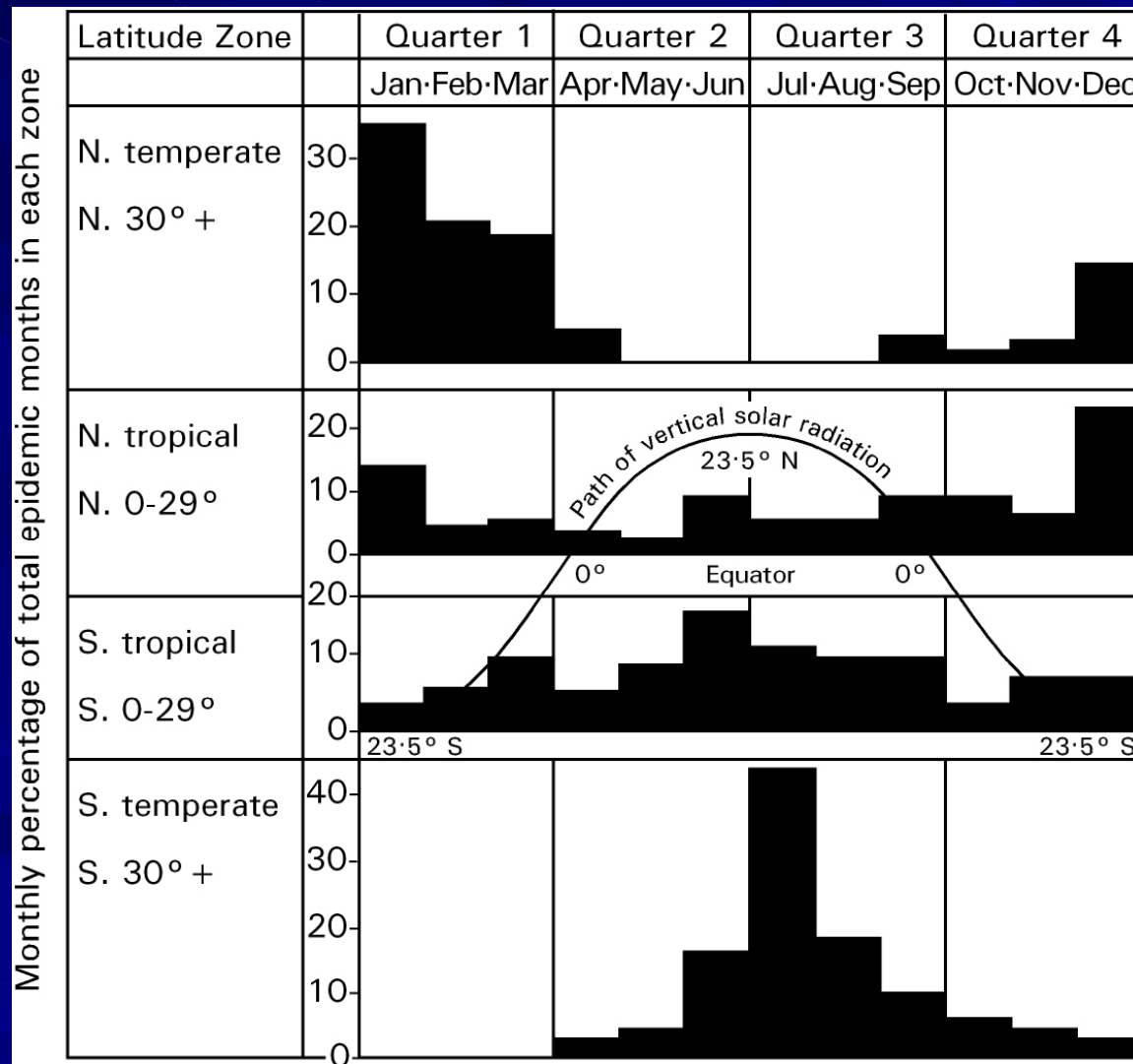
- In the 1930's, Vitamin A was investigated for its anti-infective properties using Cod liver oil, (which is also abundant in Vitamin D)
- Five studies using cod liver oil, (involving over 7,000 subjects), showed that cod liver oil reduced respiratory infections
- Cod liver oil given to 185 adults for four months reduced colds by 50%; Holmes AD, et al. Journal of Industrial and Engineering Chemistry 1932; 24: 1058-1060.
- In a five year study, cod liver reduced industrial absenteeism caused by colds and respiratory illness; days of missed work was reduced by 30%. (n=3031) Homes AD, et al. Industrial Medicine 1936; 5: 359-361.

# Influenza is a seasonal illness



Weekly consultation rates for clinically diagnosed flu

# The seasonal and latitudinal distribution of outbreaks of type A influenza in the world, 1964-1975



(WHO Data)

# Season influences the effect of inoculated influenza virus

- One study evaluated 1248 non-immune males (age 16–18 years) in northern and southern Russia during different seasons of the year.
- In the northern group, they found that the inoculated attenuated virus was about eight times more likely to cause fever in the winter than the summer (6.7% vs. 0.8%).
- In the southern area, 8% of inoculated subjects developed a fever from the virus in January, but only 0.1% did so in May.

# Season influences the effect of inoculated influenza virus. (continued)

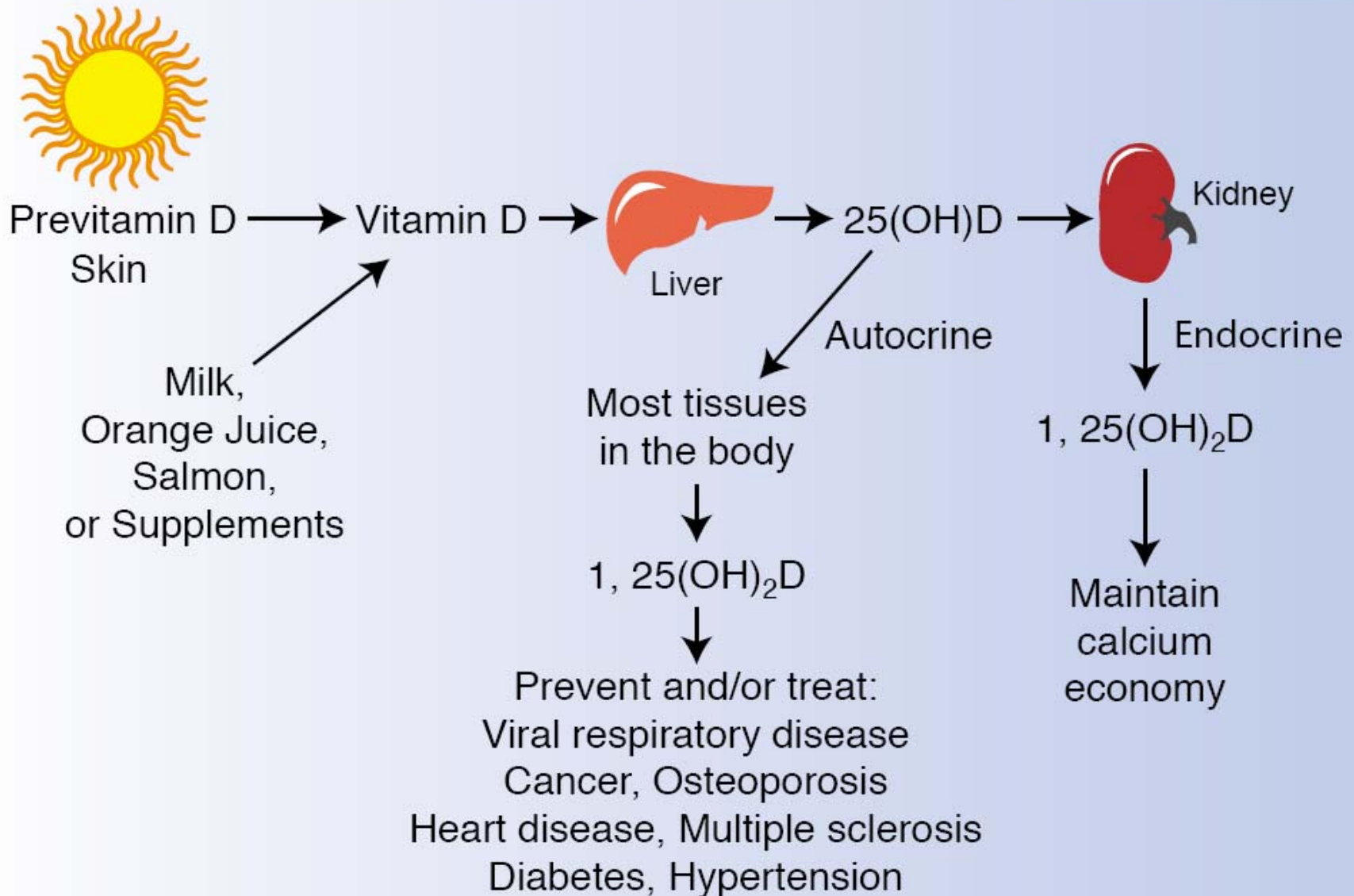
- In a replication study, seroconversion (rate of antibody formation) was found to be lowest in summer.
- Subjects were more likely to shed the virus in December (40%) than in September (16%), and the quantity of virus shed was lower in summer than winter.



# Ultraviolet Light (UVR) Effects Immunity

- A sub-erythematous dose of UVR for 6-8 weeks doubled phagocytic activity in 21 children with recurrent respiratory tract infections. Krause R, et al. In: Holick MF and Jung EG, eds. Biological Effects of Light. Kluwer Academic Publishers, 1998: pp. 49-51.
- Sub-erythematous doses of UVR (x5) increased polymorphonuclear chemotaxis in healthy volunteers. Csato M et al., British Journal of Dermatology 1984;111: 567-570.
- 410 athletes who received sub-erythematous doses of UVR (twice a year for three years) had more salivary IgA, IgG and IgM; 50% less respiratory viral infections, 300% fewer absence days and 30% shorter illness than did 446 non-irradiated control athletes. Gigineishvili GR, et al. Voprosy Kurortologii, Fizioterapii, i Lechebnoi Fizicheskoi Kultury 1990 May-Jun;(3):30-3.
- Dutch children with the most sun exposure were half as likely to develop cough, and a third as likely to develop rhinitis, compared to less sun exposed children. Termorshuizen F, et al. Photodermatology, Photoimmunology and Photomedicine 2004; 20: 270-271.

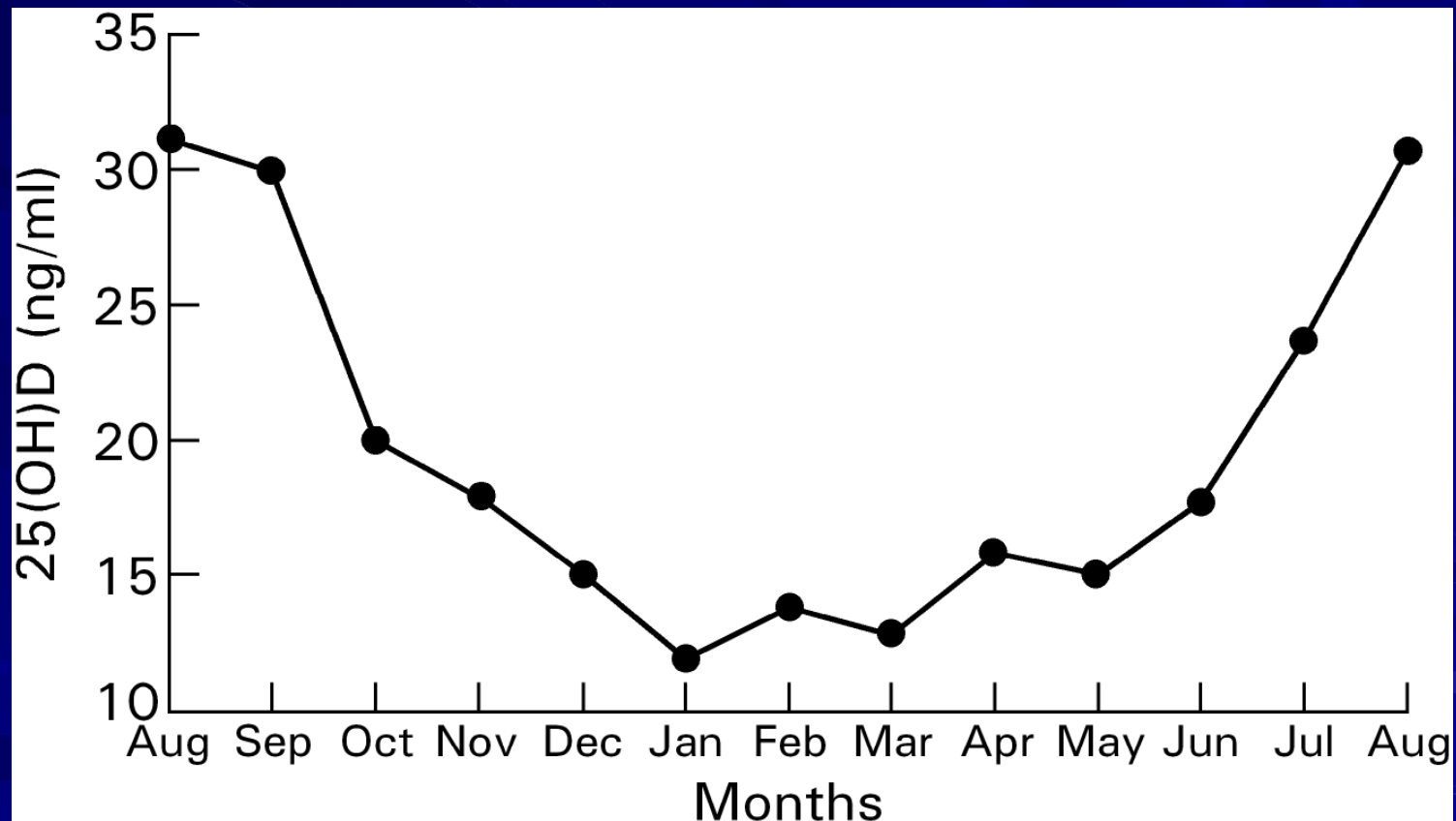
# Vitamin D Metabolism



# The Primary Source Of Vitamin D Is UVB Radiation From Sunlight

- Humans acquire most of their vitamin D from skin synthesis resulting from casual sun exposure.
- Seasonal variations - and vitamin D deficiency – occur in both subtropical and tropical latitudes.
- No vitamin D is made in the skin at latitude  $52^{\circ}$  N (the latitude of London) ~ October to March because atmospheric ozone easily filters out Ultra Violet B radiation unless the sun is high enough in the sky.

# Seasonal variation of 25(OH)D levels



# Vitamin D Effects Immunity

- Vitamin D modulates the macrophage response, preventing the release of excessive inflammatory cytokines and chemokines Hewison M, et al. Molecular and Cellular Endocrinology 2004; 215: 31-38. Helming L, et al. Blood 2005; 106: 4351-4358.
- Vitamin D promotes macrophage production of specific surface antigens, the lysosomal enzyme acid phosphatase, and the secretion of  $H_2O_2$  (which is antimicrobial), but vitamin D deficiency decreases these functions. Abu-Amer Y, Bar-Shavit Z. Cellular Immunology 1993; 151: 356-368. Cohen MS, et al. Journal of Immunology 1986; 136: 1049-1053.
- Vitamin D stimulates genetic expression of antimicrobial peptides, which have broad-spectrum antimicrobial activity and inactivate influenza virus. Wang TT, et al. Journal of Immunology 2004; 173: 2909-2912. Gombart AF et al, The FASEB Journal 2005; 19: 1067-1077. Liu PT, et al. 2006; 311: 1770-1773. Reddy KV et al, International Journal of Antimicrobial Agents 2004; 24: 536-547. Hiemstra PS, et al. Current Pharmaceutical Design 2004; 10: 2891-2905. Daher KA et al, Journal of Virology 1986; 60: 1068-1074.

Journal of Immunology 2004; 173: 2909-2912. Gombart AF et al, The FASEB Journal 2005; 19: 1067-1077. Liu PT, et al. 2006; 311: 1770-1773. Reddy KV et al, International Journal of Antimicrobial Agents 2004; 24: 536-547. Hiemstra PS, et al. Current Pharmaceutical Design 2004; 10: 2891-2905. Daher KA et al, Journal of Virology 1986; 60: 1068-1074.

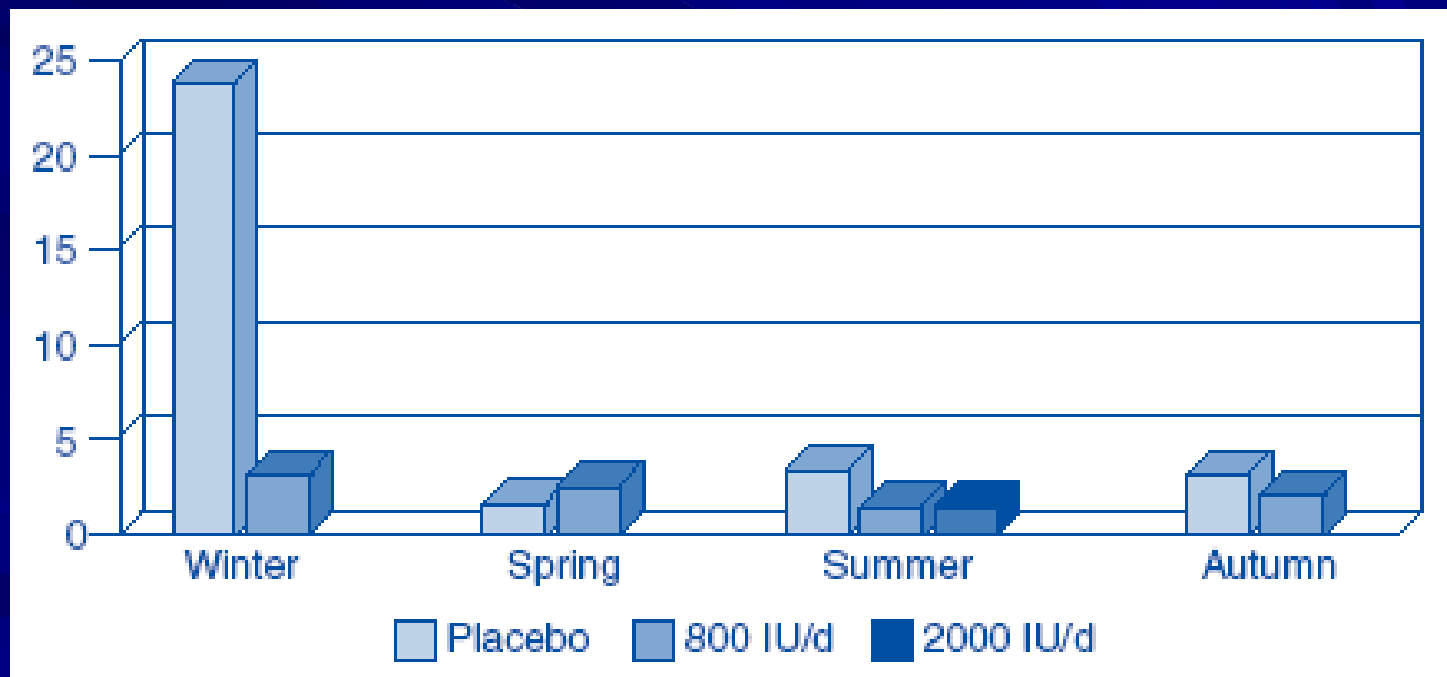


# Randomized controlled trial of vitamin D<sub>3</sub> prevent bone loss in African-American women:

- 104 women received placebo and 104 received vitamin D<sub>3</sub>.
- Vitamin D<sub>3</sub> dose was increased from 800 IU to 2000 IU after 2 years.
- Patients were followed up every 6 months for 3 years for the occurrence of adverse events, which included reports of cold and influenza.
- RESULTS: The placebo group reported 26 instances of cold and influenza vs. 8 instances in the vitamin D<sub>3</sub> group ( $P < 0.002$ ).

# Vitamin D<sub>3</sub> supplements eliminate the winter excess incidence of cold / flu

Number  
of  
patients  
reporting  
colds / flu



# How much vitamin D results from sun exposure ?

- Serum 25(OH)D levels indicate the average American gets between 50 and 1000 IU units
- 5 minutes in a bathing suit in the summer noon day sun provides about 3,000 IU.
- Melanin in the skin reduces production of vitamin D by sunlight, and African Americans have much lower 25(OH)D levels than whites
- 90% of vitamin D is obtained from the sun.



# Dietary vitamin D

- Fish is virtually the only food naturally rich in vitamin D.
- One glass of milk has 100 units, few other products are supplemented significantly.
- The current U.S. Dietary Recommended Intake of vitamin D for humans up to age 50 is 200 IU/day.
- In the absence of sun exposure, most people will become deficient

# How much vitamin D do service members get?

- No one knows.
- War fighters may get sufficient sun exposure, or their protective clothing may effectively keep them out of the sun.
- Dietary intake may be close to 200 IU/day from supplemented milk products.
- The vitamin D status of servicemembers returning from deployment could be easily measured using existing banked serum from the Defense Medical Surveillance System

# Army Rations for troops in WW I supplied ~ 500 IU of vitamin D (and ~1,300 mg of Omega -3)

A "trench ration," especially designed to meet the danger of gas contamination, was developed in 1918; it combined twenty-five rations in a single large metal container:

50 cans hard bread	8 oz. each
10 cans corned beef	16 oz. each
5 cans roast beef	16 oz. each
4 cans fish	16 oz. each
4 cans sardines	4 oz. each
25 rations sugar	5 lbs. in bulk
25 rations soluble coffee	18.75 oz.
25 rations salt	
solidified alcohol	50 oz.
25 rations cigarettes	100 cigarettes

These rations were packed by a Trench Ration Canning Department which was organized at the Chicago Quartermaster Depot and turned out its first million rations (40,000 containers) between June 12 and July 1918. The work was done on a production line basis; the components were packed in a sterilized iron container, somewhat like a wash boiler.

# Toxicity

- Vitamin D is fat soluble, and accumulation (from diet) in the body can be toxic.
- The long-term safe dose of vitamin D is not known, however, 10,000 IU /day is safe in healthy adults
- All known cases of vitamin D toxicity have involved intake of or over 40,000 IU/day.
- The LD<sub>50</sub> in man is unknown – there are no reported deaths from acute toxicity.

# Conclusion

- In addition to the established long term benefits of vitamin D, it is possible that a short term benefit of adding dietary vitamin D is to maximize readiness by reducing the incidence of colds and flu.
- The amount of vitamin D received by warfighters could be easily measured, and such measurement could guide therapy using UV light or through diet.



Times  
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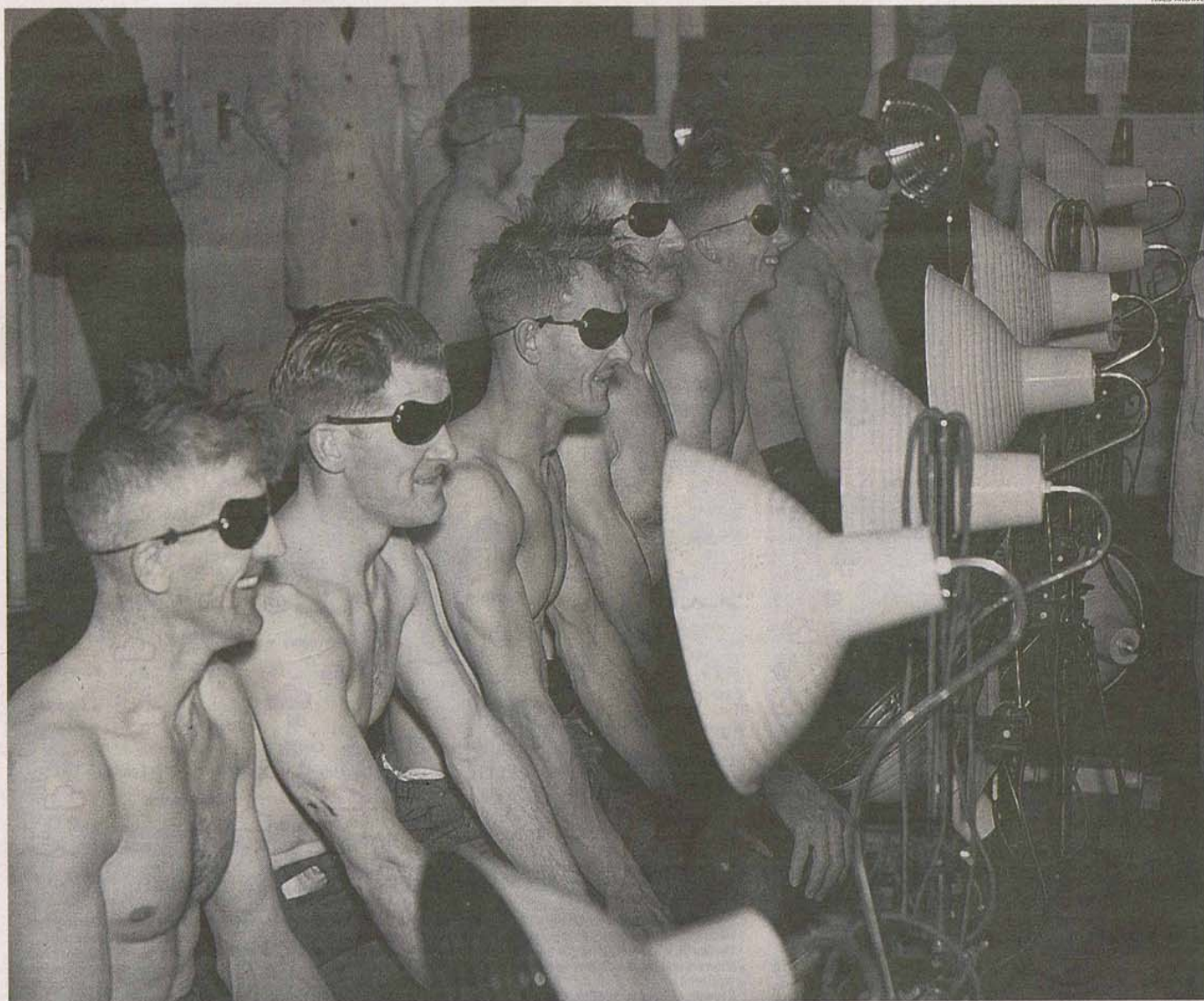
## Warming rays in postwar austerity Britain

Miners at Silverhill colliery in the Nottinghamshire coalfield supplying the vitamin deficiencies inherent in a working life spent underground with a session at the in-house solarium in September 1947. The management at Silverhill piqued itself on rates of pay and perks, which, it claimed, kept its miners contented and the pit strike-free

## Archive

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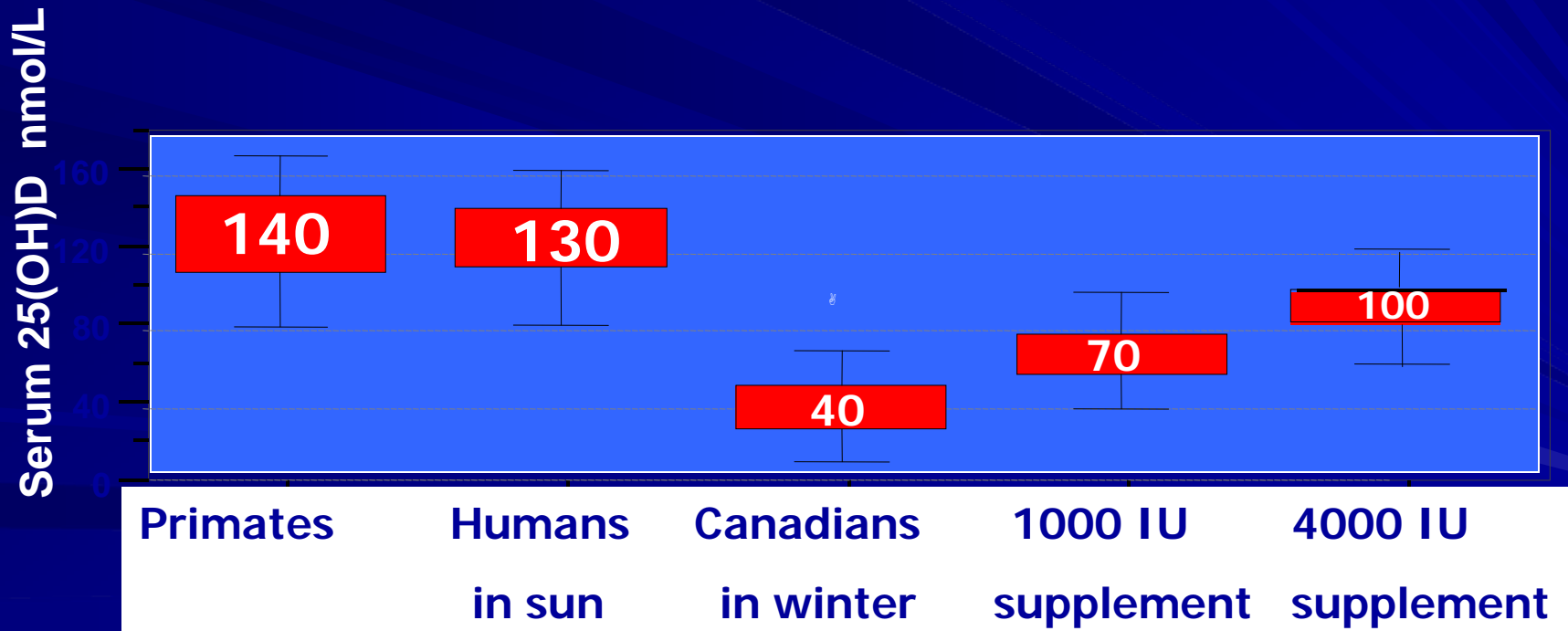
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A blood calcidiol (25-hydroxy-vitamin D) level is the accepted way to determine vitamin D nutritional status, and shows considerable variation.





# How much do we need?

- The dosage depends upon age, latitude, season, skin type, body weight, sun exposure, and preexisting 25(OH)D levels.
- When 25(OH)D levels fall below  $\sim 87\text{nmol/L}$ , calcium absorption in the intestine falls with it. That is, calcium absorption is maximized by keeping 25(OH)D levels above  $\sim 87\text{nmol/L}$ .
- Approximately 3,000 IU/day of vitamin D is required to assure that 97% of Americans obtain levels greater than  $\sim 87\text{nmol/L}$ .

# Vitamin D from sunlight affects TB

- The 1903 Nobel prize was awarded for the discovery that vitamin D from sunlight could cure cutaneous TB....